Re-evaluation Decision RVD2012-07

Fenoxaprop-P-Ethyl

(publié aussi en français)

4 June 2012

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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ISSN: 1925-1017 (print)
1925-1025 (online)

Catalogue number: H113-28/2012-7E (print version)
H113-28/2012-7E-PDF (PDF version)

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Re-evaluation Decision

After a re-evaluation of the herbicide fenoxaprop-P-ethyl, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting continued registration of products containing fenoxaprop-P-ethyl for sale and use in Canada.

An evaluation of available scientific information found that products containing fenoxaprop-P-ethyl do not present unacceptable risks to human health or the environment when used according to the revised label directions. As a condition of the continued registration of fenoxaprop-P-ethyl, new risk-reduction measures must be included on the labels of all products. Additional data are also required as a result of this re-evaluation.

The regulatory approach for the re-evaluation of fenoxaprop-P-ethyl was first presented in Proposed Re-evaluation Decision PRVD2011-04, *Fenoxaprop-P-Ethyl*, a consultation document.[1] This Re-evaluation Decision[2] describes this stage of the PMRA's regulatory process for the re-evaluation of fenoxaprop-P-ethyl as well as summarizes the Agency's decision and the reasons for it. Appendix I summarizes comments received during the consultation process and the PMRA's response to these comments. This decision is consistent with the proposed re-evaluation decision stated in PRVD2011-04. However, some mitigation measures are revised as a result of comments. Appendix III outlines the revised label amendments. To comply with this decision, registrants of products containing fenoxaprop-P-ethyl will be informed of the specific requirements affecting their product registration(s).

What Does Health Canada Consider When Making a Re-evaluation Decision?

The PMRA's pesticide re-evaluation program considers potential risks, as well as value, of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the details of the re-evaluation activities and program structure.

Fenoxaprop-P-ethyl has been re-evaluated under Re-evaluation Program 1. This program relies as much as possible on foreign reviews. For products to be re-evaluated under Program 1, the foreign review must meet the following conditions:

- it covers the main science areas, such as human health and the environment, that are necessary for Canadian regulatory decisions;
- it addresses the active ingredient and the main formulation types registered in Canada; and
- it is relevant to registered Canadian uses.

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Based on the outcome of foreign reviews and a review of the chemistry of Canadian products, the PMRA has made a regulatory decision and requires appropriate risk-reduction measures for Canadian uses of fenoxaprop-P-ethyl. In this decision, the PMRA took into account the Canadian use pattern and issues (for example, the federal Toxic Substances Management Policy [TSMP]).

The PMRA conducted a human health risk assessment for fenoxaprop-P-ethyl. A recent environmental risk assessment of fenoxaprop-P-ethyl from the European Union was found to be an adequate basis for the proposed Canadian re-evaluation decision.

Following the publication of the PRVD2011-04, changes to the registered use pattern of fenoxaprop-P-ethyl were requested by a registrant to address the risks of concern identified in the occupational and residential risk assessments. Uses on sunflower, and feed and forage crops are no longer supported. Risk assessments were updated for scenarios where the proposed changes to the registered use pattern could result in a different outcome (Appendix IV).

For more details on the information presented in this Re-evaluation Decision, please refer to the Science Evaluation Section in the related Proposed Re-evaluation Decision, PRVD2011-04, *Fenoxaprop-P-Ethyl*, and the Appendices I and IV of this decision document.

What Is Fenoxaprop-P-Ethyl?

Fenoxaprop-P-ethyl is a herbicide used to control certain annual and perennial grass weeds in cereals, certain pulse crops, vegetables, certain feed and forage crops, ryegrass grown for seeds, and turfgrass. It acts by inhibiting the synthesis of acetyl CoA carboxylase (ACCase), an enzyme required for lipid synthesis.

Following the publication of the PRVD2011-04, a registrant chose to discontinue one end-use product, Excel Super Post-Emergent Herbicide (Registration Number 21914), resulting in removing support for sunflower and feed and forage crops, and reducing maximum permitted application rates for potatoes, lentils and flax. For turf uses, the number of applications is reduced from a maximum of two to one per year.

Health Considerations

Can Approved Uses of Fenoxaprop-P-Ethyl Affect Human Health?

Fenoxaprop-P-ethyl is unlikely to affect your health when used according to the revised label directions.

People could be exposed to fenoxaprop-P-ethyl through consumption of food and water, working as a mixer/loader/applicator or by entering treated sites. The PMRA considers two key factors when assessing health risks: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human populations (for example, children and nursing mothers). Only uses for which exposure is well below levels that cause no effects in animal testing are considered acceptable for continued registration.

Maximum Residue Limits

The *Food and Drugs Act* prohibits the sale of food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Fenoxaprop-P-ethyl is currently registered in Canada for use on cereals, certain pulse crops, and vegetables and could be used in other countries on crops that are imported into Canada. MRLs have been established at 0.05 ppm for barley, wheat and dry soybean, and 0.02 ppm for milk. Where no specific MRL has been established, a default MRL of 0.1 ppm applies, which means that pesticide residues in a food commodity must not exceed 0.1 ppm. However, changes to this general MRL will be implemented in the future, as indicated in the December 2009 Information Note, *Progress on Minimizing Reliance on the 0.1 Parts per Million as a General Maximum Residue Limit for Food Pesticide Residue*.

Environmental Considerations

What Happens When Fenoxaprop-P-Ethyl Is Introduced Into the Environment?

Fenoxaprop-P-ethyl is unlikely to affect non-target organisms when used according to the revised label directions.

Birds, mammals, aquatic organisms, insects, other non-target arthropods, non-target terrestrial plants and soil non-target micro-organisms could be exposed to fenoxaprop-P-ethyl in the environment. Environmental risk is assessed by the risk quotient method-the ratio of the estimated environmental concentration to the relevant effects endpoint of concern. The resulting risk quotients are compared to corresponding levels of concern.

The European Food Safety Authority concluded that the reregistration of fenoxaprop-P-ethyl was acceptable provided risk-reduction measures to further protect the environment were implemented. These conclusions apply to the Canadian situation.

The PMRA re-calculated the buffer zones for products containing fenoxaprop-P-ethly as per the PMRA's current practice for environmental risk assessment. As a result, buffer zones are required for all uses to protect aquatic and terrestrial habitats.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human health and the environment. These directions must be followed by law. As a result of the re-evaluation of fenoxaprop-P-ethyl, the PMRA is requiring further risk-reduction measures for product labels.

Human Health

- Additional personal protective equipment to protect mixers/loaders/applicators;
- A restricted-entry interval to protect workers re-entering treated sites; and
- Prohibiting use in turf on recreational areas (excluding golf courses) and residential lawns.

Environment

- Buffer zones to protect sensitive aquatic and terrestrial habitats.

Appendix III lists all required label amendments.

Other Information

Any person may file a notice of objection[3] regarding this decision on fenoxaprop-P-ethyl within 60 days from the date of publication of this Re-evaluation Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of Health Canada's website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

[3] As per subsection 35(1) of the *Pest Control Products Act*.

Appendix I Comments and Responses

1.0 Comments Related to the Use of Historical Control Data in Mice for Assessment of Weight of Evidence of Carcinogenicity

1.1 Comment

The registrant disagrees with the carcinogenicity assessment of fenoxaprop-ethyl in male mice. The registrant provided a table summary of historical control data from four Hoechst AG studies (#1, #2, #4 and #6) relating to the incidence of type B subcapsular cell adenomas in the adrenal gland of control male Hoe:NMRKf(SPF71) mice in selected two year studies. The table included a re-evaluation of adrenal histopathology data in control male mice from each of the 4 studies, using WHO nomenclature criteria. Based on their re-evaluation of the histopathology data, the registrant presented a range of 19.6% to 52.3% for the incidence of type B subcapsular cell adenomas in the adrenal of control male mice. Since high-dose male mice treated with fenoxaprop-ethyl had a 42.9% incidence of type B subcapsular cell adenomas in the adrenal, the registrant has concluded that the incidence in high-dose males is within the range of historical controls, and thus is not treatment-related.

PMRA Response

The historical control data presented by the registrant do not contribute to the weight of evidence of carcinogenicity due to the lack of relevance of these data to the fenoxaprop-ethyl test data. The study start dates for Hoechst AG historical control study #1 (1976), #2 (1982), #4 (1978) and #6 (1985) range from 8 to 19 years from the in-life dates of the fenoxaprop-ethyl study (1993-1995), and thus are not considered to be relevant for direct comparison to the test data. The PMRA considers only historical control data derived from studies conducted within ± 5 years of the in-life dates of the test study, to ensure direct comparability.

The PMRA maintains the conclusion that there is evidence of carcinogenicity of fenoxaprop-ethyl in the adrenal gland of high-dose male Hoe:NMRKf(SPF71) mice.

2.0 Comments Related to the Assessment of Developmental Toxicity and Teratogenicity in Rats and Rabbits

2.1 Comment

The registrant disagrees with the assessment of maternal and offspring effects in the rabbit oral developmental toxicity study (1986) used for derivation of the acute dietary endpoint (PMRA# 1215556). Based on the results of this study, the PMRA derived maternal, developmental and teratogenicity NOAEL's of 32 mg/kg bw/day fenoxaprop-P-ethyl based on adverse effects in dams and offspring at 100 mg/kg bw/day. The registrant concluded that the offspring effects at 100 mg/kg bw/day are embryotoxic effects resulting from severe maternal toxicity, rather than teratogenic effects, and do not warrant an additional safety factor applied to the acute dietary risk assessment. The registrant presented a brief tabulated summary of maternal effects in this study, demonstrating a decrease in maternal food consumption and body weight gain, and an increase in maternal kidney weights at 100 mg/kg bw/day. The registrant also presented a brief tabulated

summary of historical control data for fused and/or dysplastic sternebrae in rabbits, based on a summary report which was previously submitted to the PMRA (PMRA #1230430).

PMRA Response

Effects on maternal body weight gain and food consumption, in the absence of significant effects on mean maternal body weight, are not considered to be severe effects. Similarly, an increase in maternal kidney weight, in the absence of associated functional or histopathological effects in the kidney, is not considered to be biologically adverse. Therefore, the PMRA maintains that there was only slight maternal toxicity in dams receiving 100 mg/kg bw/day fenoxaprop-P-ethyl.

Historical control data provided by the registrant for anomalies of the sternebrae in rabbits were based on the results of 58 studies conducted between 1980 and 1989, in which 46 control groups displayed longitudinally displaced, fragmented, dislocated, fused and/or dysplastic sternebrae (PMRA#1230430). Based on the results of these studies, the mean fetal control incidence for these effects is 3.3% (range = 0% to 10.9%), and the mean litter control incidence is 10.6% (range = 0% to 35.7%). It should be noted that the historical control data are not directly comparable to the test data since the historical control data include additional sternal malformations (in other words, displacement, fragmentation and dislocation) which were not observed in animals exposed to fenoxaprop-P-ethyl. In rabbits receiving 0, 10, 32 or 100 mg/kg bw/day fenoxaprop-P-ethyl, the mean incidence of fused and/or dysplastic sternebrae was 4.2%, 9.8%, 2.3% or 16.2% (fetal) and 13.3%, 21.4%, 7.1% or 38.5% (litter), respectively. Since the fetal and litter incidences of fused and/or dysplastic sternebrae in rabbits receiving 100 mg/kg bw/day fenoxaprop-P-ethyl are greater than the combined historical control incidences for multiple defects in the sternebrae (including fused or dysplastic sternebrae), the malformations noted at 100 mg/kg bw/day are considered to be treatment-related.

For assessment of renal malformations, a summary of historical control data for transverse position or displacement of the kidney in the offspring of rabbits was previously provided by the registrant (PMRA #1225015). The summary data were based on the results of 50 historical control studies conducted between 1979 and 1987, in which 40 control groups displayed transverse position or displacement of the kidney. Based on the results of these studies, the mean fetal historical control incidence for these effects is 2.2% (range = 0% to 9%), and the mean litter historical control incidence is 12.3% (range = 0% to 40%). In the fenoxaprop-P-ethyl study, rabbits receiving 0, 10, 32 or 100 mg/kg bw/day had transverse position or displacement of the kidney at a mean incidence of 2.1%, 0%, 2.3% or 10.8% (fetal) and 6.7%, 0%, 7.1% or 30.8% (litter), respectively. Although the litter incidence in treated high-dose animals (30.8%) is within the range of historical controls (i.e., 0% to 40%), there is concern since the litter incidence in treated animals exceeds both the mean historical control incidence (12.3%) and the concurrent control incidence (6.7%). The similarity of mean historical control values (fetal and litter) with concurrent control values supports the comparison of treatment groups with concurrent controls, and confirms the treatment-related increase in kidney malformations in rabbits exposed to 100 mg/kg bw/day fenoxaprop-P-ethyl.

The kidney displacement and other severe visceral malformations (diaphragmatic hernias, abdominal fissures/clefts, protrusion of intestines, lung lobe fusion, and heart defects) noted in rabbits and rats exposed to fenoxaprop-P-ethyl or fenoxaprop-ethyl (D/L racemic mixture) are consistent with the known profile for congenital diaphragmatic hernia. Congenital diaphragmatic hernia is a large defect in the posterior or posterolateral region of the diaphragm, near the kidney.

Failure in the fusion of the pleuroperitoneal membranes with other components of the diaphragm results in the migration of the kidney, intestines, stomach and liver into the thoracic cavity and displacement of the heart and lungs. Treatment-related diaphragmatic hernias have also been noted in the offspring of rabbits dermally-exposed to a maternally-toxic dose. It is noteworthy that treatment-related diaphragmatic hernias and skeletal defects have been reported in oral teratology studies conducted in rats with structurally-similar compounds, including diclofop-methyl and fluazifop-butyl.

Therefore, based on the weight of evidence, the PMRA retains the teratogenicity NOAEL in rabbits of 32 mg/kg bw/day fenoxaprop-P-ethyl, based on treatment-related renal and skeletal malformations at 100 mg/kg bw/day, in the presence of slight maternal toxicity. Where this NOAEL is considered critical for risk assessment purposes (in other words, ARfD for females 13+), a 3-fold PCPA factor has been applied for concerns relating to the young (See Section 5.0 for discussion of PCPA Hazard Characterization).

2.2 Comment

The registrant disagrees with the assessment of teratogenicity and selection of offspring NOAEL's in the critical rat developmental toxicity study (PMRA# 1215554) used for short- and intermediate-term dermal and inhalation risk assessment in adults. Based on the results of this study, the PMRA selected a developmental NOAEL of 10 mg/kg bw/day (based on delayed ossification of cranial bones at 32 mg/kg bw/day), a teratogenicity NOAEL of 32 mg/kg bw/day (based on visceral and skeletal malformations at 100 mg/kg bw/day) and a maternal NOAEL of 32 mg/kg bw/day. The registrant considers the developmental NOAEL in rats to be 32 mg/kg bw/day, based on an in-house historical control range of 13.1% to 56% (mean = 31 ± 9.6%) for delayed ossification of cranial bones (supplement to document No. A37496). The registrant has concluded that there is no evidence of teratogenicity in rats, and has presented a brief summary of historical control data for dysplastic/dislocated sternebrae. The registrant does not consider the 3-fold factor applied for short- and intermediate-term dermal and inhalation risk assessment in adults to be warranted, since fetotoxic effects in the critical study were observed in the presence of maternal toxicity.

PMRA Response

Effects on maternal body weight gain and food consumption, in the absence of significant effects on mean maternal body weight, are not considered to be severe effects. Similarly, a decrease in maternal heart weight, in the absence of associated clinical pathology or histopathological effects, is not considered to be biologically adverse. Therefore, the PMRA maintains that there was only slight maternal toxicity in dams receiving 100 mg/kg bw/day fenoxaprop-P-ethyl.

Study-specific details regarding the in-house historical control data for delayed ossification of cranial bones in rats were not presented by the registrant. Following re-examination of the fenoxaprop-P-ethyl study data, the PMRA has confirmed the developmental NOAEL of 10 mg/kg bw/day, based on a dose-related statistically-significant increase in the incidence and severity of delayed ossification of the cranial bones in live rat fetuses at ≥ 32 mg/kg bw/day. The incidence of delayed ossification of cranial bones in live rat fetuses receiving 0, 10, 32 or 100 mg/kg bw/day fenoxaprop-P-ethyl was 19.5%, 30.5% ($p<0.05$), 56.8% ($p<0.05$) or 65.5% ($p<0.05$), respectively. The corresponding litter incidence was 60%, 65%, 84.2% or 88.9%, respectively. While delayed ossification of cranial bones was not specifically examined in dead

fetuses in this investigation, delayed ossification of the entire skeleton in dead fetuses receiving 32 mg/kg bw/day (1/1) or 100 mg/kg bw/day (2/2) was noted by the study authors. Treatment-related delayed ossification of the entire skeleton was also noted in another oral developmental toxicity study in rats (PMRA# 1199542). The PMRA retains the developmental NOAEL of 10 mg/kg bw/day fenoxaprop-P-ethyl, based on delayed ossification of the cranial bones in rats.

For assessment of sternal malformations, historical control data derived from 56 studies conducted in Wistar rats between 1980 and 1989 were previously provided by the registrant (PMRA#1230426). Longitudinally displaced, dysplastic, dislocated or fragmented sternebrae were noted in control rats in 47 of these studies. Based on the results of all studies, the mean fetal historical control incidence is 2.4% (range = 0% to 7.6%), while the mean litter historical control incidence is 12.0 % (range = 0% to 40%). In the fenoxaprop-P-ethyl study, rats receiving 0, 10, 32 or 100 mg/kg bw/day had an incidence of 1.5%, 2.3%, 0.8% or 23.6% ($p<0.05$) (fetal) and 5%, 10%, 5.3% or 66.7% ($p<0.05$) (litter) for longitudinally displaced, dysplastic, dislocated, fused or fragmented sternebrae. The similarity of mean historical control data (litter and fetal) with concurrent control values supports the comparison of treatment groups with concurrent controls, and confirms the increased fetal and litter incidences of malformations following exposure to 100 mg/kg bw/day fenoxaprop-P-ethyl.

For assessment of vertebral malformations, historical control data from 52 studies conducted in Wistar rats between 1980 and 1989 were previously provided by the registrant (PMRA#1230426). Fragmented and/or dislocated thoracic vertebral centra were observed in control rats in 21 of these studies. Based on the results of all studies, the mean fetal historical control incidence for these effects is 0.4% (range = 0% to 2.4%), while the mean litter historical control incidence is 3.1% (range = 0% to 15.8%). Wistar rats exposed to 0, 10, 32 or 100 mg/kg bw/day fenoxaprop-P-ethyl had a fetal incidence of 0%, 0.8%, 0% or 3.6% for fragmented and/or dislocated thoracic vertebral centra, while the litter incidence for these effects was 0%, 5%, 0% or 11.1%. Although the litter incidence (11.1%) in treated high-dose animals is within the range of historical controls (0% to 15.8%), there is concern since this incidence exceeds both the mean historical control (3.1%) and concurrent control values (0%). The similarity of mean historical control and concurrent control values supports the comparison of treatment groups with concurrent controls, and confirms the increased fetal and litter incidences of malformations of the vertebrae following exposure to 100 mg/kg bw/day fenoxaprop-P-ethyl.

For assessment of visceral malformations, historical control data from 56 studies conducted in Wistar rats between 1980 and 1986 were previously provided by the registrant (PMRA#1230426). Abdominal fissures with protruding liver and intestines were observed in control rats in one study only. When the results of all studies are considered, the mean fetal control incidence for these effects is 0.007% (range= 0% to 0.4%) and the mean litter control incidence is 0.09% (range= 0% to 5.3%). Wistar rats exposed to 0, 10, 32 or 100 mg/kg bw/day fenoxaprop-P-ethyl had a fetal incidence of 0%, 0%, 0% or 1% for abdominal fissures with protruding liver and intestines, and a litter incidence of 0%, 0%, 0% or 5.6% for these effects. Although fetal and litter incidences in treated high-dose animals only slightly exceed the range of historical controls, there is concern since these incidences exceed both the mean historical control and concurrent control values. The similarity of mean historical control and concurrent control values supports the relevance of concurrent controls for comparison with the treatment groups, and confirms the increased fetal and litter incidences of visceral malformations following exposure to 100 mg/kg bw/day fenoxaprop-P-ethyl.

As discussed previously in Section 2.1, the skeletal and visceral malformations observed in rats and rabbits are consistent with a syndrome of developmental toxicity associated with exposure to fenoxaprop-P-ethyl or fenoxaprop-ethyl. Similar malformations have been noted in oral developmental toxicity studies conducted in rats with structurally-related compounds. In view of the weight of evidence, the PMRA retains the teratogenicity NOAEL of 32 mg/kg bw/day fenoxaprop-P-ethyl in the critical rat developmental toxicity study, based on treatment-related visceral and skeletal malformations.

Where this oral developmental toxicity study is critical for risk assessment purposes (in other words, short- and intermediate-term inhalation risk assessment in adults), a 3-fold PCPA factor has been applied to the risk assessment for concerns relating to the young (See Section 5.0 for discussion of PCPA Hazard Characterization).

3.0 Comments Related to the Short- and Intermediate-Term Dermal Risk Assessment for Children and Adults

3.1 Comment

The registrant disagrees with the statement that the short-term dermal toxicity study in rats is not protective to children. This study was conducted by a relevant route in a relevant population (6-week old rats), the results suggest low toxicity via the dermal route, and effects were qualitatively similar to those in short- and intermediate-term oral studies suggesting adequate dose selection and characterization of dose-response. The short-term dermal NOAEL should be used for short-term dermal risk assessment in children.

If developmental toxicity is considered to be the finding of concern for short- and intermediate-term dermal risk assessment of women of childbearing age, the dermal developmental toxicity studies should be used for short- and intermediate-term dermal risk assessment for this population.

PMRA Response

The short-term dermal risk assessment for children will be revised based on the dermal NOAEL of 20 mg/kg bw/day derived in the short-term dermal toxicity study in rats (PMRA#1239331), since sensitivity is not a concern for this population. A Target Margin of Exposure of 100 is selected based on standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability. The PCPA factor is reduced to 1-fold, since concerns for the young are associated with *in-utero* exposure only.

The short- and intermediate-term dermal risk assessments for adults (including pregnant females) will be revised based on the maternal LOAEL of 100 mg/kg bw/day derived in the dermal developmental toxicity study in rats, based on reduced body weight in dams during treatment. The Target Margin of Exposure is 300, which includes standard uncertainty factors of 10-fold for inter-species extrapolation, 10-fold for intra-species variability and 3-fold for lack of a NOAEL. For residential scenarios, the PCPA factor is reduced to 1-fold since the selected endpoint and MOE provide an adequate margin of 900 to the NOAEL of 300 mg/kg bw/day for teratogenicity in the rabbit dermal study (in the presence of maternal toxicity).

4.0 Comments Related to the Inhalation Risk Assessment for Children

4.1 Comment

The registrant disagrees with the statement that the short-term inhalation toxicity study in rats is not protective for inhalation risk assessment in children. The 28-day inhalation toxicity study in rats is appropriate since it was conducted in a relevant population (5-6 week old rats), and effects were qualitatively similar to those in oral and dermal studies suggesting adequate dose-selection and characterization of dose-response. The short-term inhalation NOAEL should be used for short-term inhalation risk assessment in children.

PMRA Response
The short-term inhalation risk assessment for children will be revised based on the inhalation NOAEL of 19 mg/kg bw/day (NOAEC= 0.07 mg/L) derived in the 28-day inhalation toxicity study in rats (PMRA#1239332), since sensitivity is not a concern for this population. A Target Margin of Exposure of 100 is selected based on standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability. The PCPA factor is reduced to 1-fold since concerns for the young are associated with *in-utero* exposure only.

5.0 PCPA Hazard Characterization

In view of the new policy on the use of uncertainty factors and the PCPA factor, the PMRA has re-examined the factors used for risk assessment of fenoxaprop-P-ethyl. For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account the completeness of the data with respect to the exposure of, and toxicity to, infants and children as well as potential pre- and post-natal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicology database for the assessment of risk to infants and children, there is an adequate range of studies including acceptable oral developmental toxicity studies in mice, rats, rabbits, a supplemental developmental toxicity study in monkeys, adequate dermal developmental toxicity studies in rats and rabbits, and an acceptable 2-generation reproductive toxicity study in rats. Developmental neurotoxicity and comparative acute neurotoxicity studies in experimental species are not available, however neurotoxic effects have not been consistently observed in the database.

With respect to identified concerns relevant to the assessment of risk to the young, the fetus may be more susceptible to fenoxaprop-P-ethyl, compared to adults, based on evidence of sensitivity in oral developmental toxicity studies in rats and rabbits. Skeletal variations were observed in rat fetuses in the absence of maternal toxicity, following exposure to fenoxaprop-P-ethyl or fenoxaprop-ethyl (D/L racemic mixture). At oral doses of fenoxaprop-P-ethyl (or D/L racemic mixture) which induced only slight maternal toxicity, increased fetal resorptions, visceral malformations (diaphragmatic hernias, abdominal fissures/clefts, protrusion of intestines, kidney displacement, lung lobe fusion, and heart defects) and vertebral and sternebrae effects (fragmentations, dislocations, displacements, fusions) were also observed in fetal rats and rabbits. Treatment-related diaphragmatic hernias were also noted in the fetuses of rabbits

dermally-exposed to a maternally-toxic dose. No evidence of sensitivity of the young was noted in the reproductive toxicity study.

For risk assessment in adults, the fetal effects (in other words, resorptions and malformations) observed in the developmental toxicity assays were considered serious endpoints although the concern was tempered by the presence of maternal toxicity. Therefore, the PCPA factor has been reduced to 3-fold when using the developmental toxicity assay to establish the point of departure for women of childbearing age. The PCPA factor was reduced to 1-fold for other risk assessment scenarios as the selected endpoints provide adequate margins to developmental endpoints.

For risk assessment in children, the PCPA factor is reduced to 1-fold, since concerns for the young are associated with *in-utero* exposure only.

6.0 Reference Doses

The PMRA has re-examined the reference doses for fenoxaprop-P-ethyl in light of the policy on the use of uncertainty factors and the PCPA factor.

Acute Reference Dose (ARfD)

ARfD (females 13+):

For derivation of the ARfD, the assessment has been based on malformations in developmental toxicity studies conducted with fenoxaprop-P-ethyl, assuming these effects may arise from a single exposure. The ARfD is relevant to women of child-bearing age. No ARfD has been established for other populations, since there was no relevant endpoint of concern attributable to a single dose.

To estimate acute dietary risk, the NOAEL of 32 mg/kg bw/day was selected from an oral developmental toxicity study in rabbits with fenoxaprop-P-ethyl. This NOAEL was based on visceral and skeletal malformations in fetuses at 100 mg/kg bw/day, in the presence of slight maternal toxicity. This was supported by consistent evidence of teratogenicity in other developmental toxicity studies conducted with either fenoxaprop-P-ethyl or the D/L mixture. A composite assessment factor of 300 has been applied to the NOAEL to account for inter-species extrapolation (10-fold), inter-species variability (10-fold), and a 3-fold PCPA factor for concerns relating to the young. (See PCPA Hazard Characterization Section)

$$\textbf{ARfD} = \frac{\textbf{32 mg/kg bw}}{\textbf{300}} = \textbf{0.10 mg/kg bw}$$

This reference dose is the same value as that outlined in the PRVD.

Acceptable Daily Intake (ADI)

ADI (general population including children):
To estimate dietary risk of repeat exposure, the NOAEL of 0.4 mg/kg bw/day for fenoxaprop-ethyl (D/L racemic mixture) in a 2-year oral toxicity study in dogs (a sensitive species) was selected. Reduced body weight gain, haematological changes and increased relative kidney and liver weights were observed in both sexes at the next dose (LOAEL= 1.9 mg/kg bw/day). Application of a composite assessment factor of 100 (10-fold for inter-species extrapolation, 10-fold for intra-species variability, and 1-fold for PCPA) to the NOAEL results in an ADI of **0.004 mg/kg bw/day**.

This ADI provides a margin of 375 to the offspring NOAEL (1.5 mg/kg bw/day) in rat pups in the 2-generation reproductive toxicity study conducted with the D/L racemic mixture, and a margin of 2500 to the lowest NOAEL (10 mg/kg bw/day in rats) for developmental toxicity (skeletal effects) of fenoxaprop-P-ethyl. Also, the ADI provides a margin of 375 to the NOAEL of 1.5 mg/kg bw/day in the chronic dietary study in mice (another sensitive species) conducted with the D/L racemic mixture.

This reference dose is the same value as that outlined in the PRVD.

Toxicology Endpoint Selection for Occupational and Bystander Risk Assessment

Dermal Exposure

For assessment of **short- and intermediate-term dermal risk for children,** the 30-day dermal toxicity study in rats was selected, in which a dermal NOAEL of 20 mg/kg bw/day was derived based on liver and kidney effects at the LOAEL. Since 6-week old rats were directly exposed by a relevant route and duration of exposure, this investigation is considered most relevant to assessment of short-term risk for children. The liver and kidney effects in the short-term dermal study are consistent with effects observed in offspring and parents receiving the D/L mixture in the oral multi-generation reproductive toxicity study, and sensitivity is not a concern for this population. A Target Margin of Exposure of 100 is selected based on standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability. The PCPA factor is reduced to 1-fold, since concerns for the young are associated with *in-utero* exposure only.

For assessment of **short- and intermediate-term dermal risk for adults (including pregnant women),** the dermal developmental toxicity study in Wistar rats was selected, in which a maternal LOAEL of 100 mg/kg bw/day was derived based on reduced body weight during treatment. The Target Margin of Exposure is 300, which includes standard uncertainty factors of 10-fold for inter-species extrapolation, 10-fold for intra-species variability and 3-fold for lack of a NOAEL. For residential scenarios, the PCPA factor is reduced to 1-fold since the selected endpoint and MOE provide an adequate margin of 900 to the NOAEL for teratogenicity in the rabbit dermal developmental toxicity study (in the presence of maternal toxicity).

Since the oral toxicity of fenoxaprop-P-ethyl increases with increasing duration of exposure and long-term dermal studies have not been identified, the **long-term dermal risk assessment** has been based on the chronic dietary assay in dogs. In this study, reduced body weight gain, haematological changes and increased relative kidney and liver weights were observed at the LOAEL of 1.9 mg/kg bw/day; the NOAEL in this study was 0.4 mg/kg bw/day. The target Margin of Exposure (MOE) is 100, accounting for standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability. For residential scenarios, the PCPA factor is reduced to 1-fold, since the NOAEL and MOE are considered inherently protective of potential developmental effects as they provide a margin of >2000 to developmental NOAEL's. The endpoint and MOE are the same as those outlined in the PRVD.

Inhalation Exposure

For assessment of **short-term inhalation risk for children,** the 28-day inhalation toxicity study in Wistar rats was selected, in which a NOAEL of 19 mg/kg bw/day was derived based on adverse liver and kidney effects at the LOAEL. Since 5- to 6-week old rats were directly exposed by a relevant route and duration, this investigation is considered most appropriate for assessment of short-term inhalation risk for children. Effects in the kidney and liver in this study are consistent with kidney and liver effects in offspring and parents receiving the D/L mixture in the multi-generation oral reproductive toxicity study in rats, and sensitivity is not a concern for this population. The target Margin of Exposure (MOE) is 100, accounting for standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability. The PCPA factor is reduced to 1-fold since concerns for the young are associated with *in-utero* exposure only.

For **assessment of short- or intermediate-term inhalation risk for adults,** the oral developmental toxicity study in rats with fenoxaprop-P-ethyl was selected, in which a NOAEL of 10 mg/kg bw/day was derived based on a dose-related increase in the incidence and severity of delayed ossification of cranial bones in offspring at ≥32 mg/kg bw/day fenoxaprop-P-ethyl, in the absence of maternal toxicity. Although only one site was developmentally-delayed in the critical study, the importance of the cranium, along with the prominence of developmental toxicity throughout the database contributes to the weight of evidence in using this endpoint for risk assessment. The target Margin of Exposure (MOE) is 100, accounting for standard uncertainty factors of 10-fold for both inter-species extrapolation and intra-species variability. For residential scenarios, the PCPA factor is reduced to 1-fold, since delayed ossification of the cranium is not considered to be a severe endpoint.

Since the oral toxicity of fenoxaprop-P-ethyl increases with increasing duration of exposure and long-term inhalation studies were not identified, **the long-term inhalation risk assessment for adults** was based on the NOAEL of 0.4 mg/kg bw/day fenoxaprop-ethyl (D/L racemic mixture) which was derived in an adequate 2-year oral toxicity study in dogs. Reduced body weight gain, haematological changes and increased relative kidney and liver weights were noted at the LOAEL of 1.9 mg/kg bw/day. The target Margin of Exposure (MOE) is 100, accounting for standard uncertainty factors of 10-fold for both inter-species extrapolation and intra-species variability. For residential scenarios, the PCPA factor is reduced to 1-fold, since the NOAEL and MOE are considered inherently protective of potential developmental effects. The endpoint and MOE are the same as those outlined in the PRVD.

Non-Dietary Oral Ingestion

Acute oral reference doses (1-day) were not required due to the low acute toxicity of fenoxaprop-P-ethyl. For short-term oral exposure (1-30 days), the oral two-generation reproductive toxicity study in rats receiving the D/L racemic mixture was selected, in which parental and offspring NOAEL's of 1.5 mg/kg bw/day were derived. Since young animals in this study were directly exposed during lactation and weaning for a relevant duration, this investigation is considered most relevant to assessment of short-term oral risk for children. The target Margin of Exposure (MOE) is 100, accounting for standard uncertainty factors of 10-fold for both inter-species extrapolation and intra-species variability. The PCPA factor was reduced to 1-fold, since concerns for the young are associated with *in-utero* exposure only. The endpoint and MOE are the same as those outlined in the PRVD.

7.0 Comment Related to Residential Post-Application Exposure Assessment

The registrant has requested a reduction in the number of applications for turf from a maximum of two to one per year. A revised risk assessment was requested.

PMRA Response

The exposure and risk estimates for post-application activities on turf in recreational areas (for example, public areas, school yards and parks) and golf courses were updated to reflect the reduced number of applications. Updated assessments also included the revised endpoint for dermal exposure. For the cancer assessment, the exposure duration per year was reduced from 30 days to 15 days in consideration of the reduction in application frequency.

Residential Post-application Non-Cancer Risk Assessment

The results of the fenoxaprop-P-ethyl residential post-application non-cancer risk assessment are summarized in Appendix IV, Table 2. The calculated MOEs from post-application exposure are greater than the target MOEs of 100 or 300, and therefore risks are not of concern.

Residential Post-application Cancer Risk Assessment

The results of the fenoxaprop-P-ethyl residential post-application cancer risk assessment are summarized in Appendix IV, Table 3. Cancer risk from post-application exposure is below the threshold of 1×10^{-6} for golfers and therefore is not of concern. However, cancer risk is above the threshold of 1×10^{-6} for recreational and residential exposure and therefore remains of concern.

Therefore, the use of fenoxaprop-P-ethyl on recreational areas (excluding golf courses) and residential lawns can not be supported.

8.0 Comments Related to Turf Application Using High Pressure Hand Wand

The registrant has requested a reduction in the number of applications for turf from a maximum of two to one per year. In addition, use information was provided indicating that fenoxaprop-P-ethyl is typically applied to golf course turf once a year, and hand held applications are unlikely to exceed 10 times per year. Hand held equipment is also unlikely to be used on sod farms. The registrant has therefore requested the Agency reconsider eliminating the application of fenoxaprop-P-ethyl using high pressure hand wand.

PMRA Response
A revised risk assessment was conducted for occupational M/L/A on turf by high pressure hand wand, based on the revised occupational exposure endpoints, and the decreased number of applications per year. Considering that golf course workers typically apply pesticide themselves, rather than custom applicators, the treatment frequency of 15 days per year is used in the updated M/L/A risk assessment for golf courses; however, the treatment frequency was maintained at 30 days for custom applicators for recreational areas and residential lawns to account for exposure to custom applicators.

The results of the fenoxaprop-P-ethyl occupational M/L/A non-cancer risk assessment for turf application, using high pressure hand wand are summarized in Appendix IV, Table 4. The calculated MOEs for M/L/A exposure are greater than the target MOE of 300, and therefore risks are not of concern.

The results of the cancer risk assessments for turf application using high pressure hand wand are summarized in Appendix IV, Table 5. The M/L/A cancer risk is 1×10^{-5} for golf courses and therefore is not of concern. However, cancer risk is above the threshold of 1×10^{-5} for M/L/A in recreational areas and residential lawns and therefore remains of concern.

The label amendment has been revised based on the revised assessment. Turf application using high pressure hand wand on golf courses is supported, however, not in residential areas and in residential lawns.

9.0 Comments Related to Turf Farms/Commercial Non-Residential Turf Areas/Golf Courses

A comment was received requesting that the PMRA reconsider the transfer coefficients (TCs) used in theses assessments.

PMRA Response
The postapplication risk assessment was updated to include the TC of 3500 cm^2/hour for mowing and transplanting. The treatment frequency was revised to 15 days in consideration of the reduction in application frequency. Updated assessments also included the revised toxicological endpoints.

The results of the fenoxaprop-P-ethyl occupational post-application non-cancer risk assessment are summarized in Appendix IV, Table 6. The calculated MOEs from post-application exposure are greater than the target MOE of 300, and therefore risks are not of concern.

The results of the fenoxaprop-P-ethyl occupational post-application cancer risk assessments are summarized in Appendix IV, Table 7. The post-application risk at day 0 is below the threshold of 1×10^{-5} and therefore is not of concern.

A 12 hour re-entry interval is required for turf uses on sod farms as per the PMRA's general practice. For golf courses, a statement of "do not enter treated areas until sprays have dried" is required.

10.0 Comments Related to the Limit Amount Proposed for Potatoes, Lentils, Flax, Sunflower, Feed and Forage Crops.

The registrant has requested that the PMRA reconsider the proposed limits on the amount handled per day for potatoes, lentils, flax, sunflower, given the discontinuation of the product, Excel Super Post-Emergent Herbicide (Registration Number 21914).

PMRA Response
Excel Super Post-Emergent Herbicide (Registration Number 21914) was discontinued as of April 5, 2011. As a result of the discontinuation of this product, there are no longer registered uses on sunflower, and feed and forage crops. In addition, the maximum permitted application rate for potatoes, lentils and flax is reduced. Therefore, a revised assessment was conducted for uses in potatoes, lentils and flax.

The results of the fenoxaprop-P-ethyl occupational M/L/A non-cancer risk assessment are summarized in Appendix IV, Table 8. The calculated MOEs from M/L/A exposure are greater than the target MOEs of 100 or 300, and therefore risks are not of concern.

The results of the fenoxaprop-P-ethyl occupational M/L/A cancer risk assessments are summarized in Appendix IV, Table 9. The risk at day 0 is below the threshold of 1×10^{-5} and therefore is not of concern.

The label amendment has been revised. Based on the revised assessment, there are no restrictions required to the amount handled per day for uses on potatoes, lentils and flax.

11.0 Comments Related to the Proposed REI on Flax, Broccoli, Cabbage and Cauliflower

The registrant has requested that the PMRA reconsider the proposed REIs for uses on flax, broccoli, cabbage and cauliflower, given the discontinuation of the product, Excel Super Post-Emergent Herbicide (Registration Number 21914).

PMRA Response

Excel Super Post-Emergent Herbicide (Registration Number 21914) was discontinued as of April 5, 2011. As a result of the discontinuation of this product, the maximum permitted application rate for flax, broccoli, cabbage and cauliflower is reduced. An updated postapplication assessment was conducted.

The results of the fenoxaprop-P-ethyl occupational post-application non-cancer risk assessment are summarized in Appendix IV, Table 10. The calculated MOEs from post-application exposure are greater than the target MOE of 300, and therefore risks are not of concern.

The results of the fenoxaprop-P-ethyl occupational post-application cancer risk assessments are summarized in Appendix IV, Table 11. The post-application risk at day 0 is below the threshold of 1×10^{-5} and therefore is not of concern.

The label amendment has been revised. Based on the revised assessment, a 12 hour re-entry interval is required for agricultural uses as per the PMRA's general practice.

Appendix II Additional Data Requirements

The following data are required as a condition of continued registration under Section 12 of the *Pest Control Products Act*. The registrants of technical products are required to provide these data within the timeline specified in the decision letter that will be sent to registrants by the PMRA.

DACO 2.13.4 Impurities of human health or environmental concern

The registrants of products Registration Numbers 21903, 29250, 29325 and 29742 must submit recent analytical data from at least five batches of TGAI for all identifiable dioxins and furans, from a GLP-compliant or government-accredited laboratory. The report should include data for the 17 substances listed in Table 4 of the Priority Substances List 1 document "Polychlorinated dibenzodioxins and polychlorinated dibenzofurans", found at: http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl1-lsp1/dioxins_furans_dioxines_furannes/index-eng.php. The analytical method(s) used must utilize the lowest practical limits of quantitation and be fully specified, either by reference to a standard method or by inclusion of a detailed description together with validation data.

Appendix III Label Amendments for Products Containing Fenoxaprop-P-Ethyl

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the label statements below.

The labels of end-use products in Canada must be amended to include the following statements to further protect workers and the environment.

I) The following statements must be included in a section entitled PRECAUTIONS of all end-use products.

- Gloves must be worn during mixing and loading

II) For products registered for agricultural uses, the following statements must be included in a section entitled PRECAUTIONS.

- DO NOT enter or allow worker entry into treated areas during the restricted entry interval of 12 hours

III) For products registered for turf uses, Registration Numbers 22886 and 21925:

i) Under the section entitled **DIRECTIONS FOR USE**,

Remove all instructions related to a second application, including the following

"Heavy monostands of mature or maturing annual grassy weeds may require a second application 21 days after the first application to achieve complete control. Second applications may cause an initial slight reduction in turf vigour."

Add the following statements:

- DO NOT make more than one application per year.
- DO NOT apply on recreational areas (excluding golf courses) and residential lawns.

ii) Under the section entitled PRECAUTIONS,

Add the following statement:

- For sod farms, DO NOT enter or allow worker entry into treated areas during the restricted entry interval of 12 hours

- For golf courses, DO NOT enter treated areas until sprays have dried.

IV) The following statements must be included in a section entitled ENVIRONMENTAL HAZARDS.

TOXIC to aquatic organisms and non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.

V) Add to DIRECTIONS FOR USE:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification. Boom height must be 60 cm or less above the crop or ground.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification. To reduce drift caused by turbulent wingtip vortices, the nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing- or rotorspan.

Buffer zones:

Use of the following spray methods or equipment **DO NOT** require a buffer zone: hand-held or backpack sprayer and spot treatment.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands) and sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands).

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:		
			Freshwater Habitat of Depths:		Terrestrial habitat
			Less than 1 m	Greater than 1 m	
Field sprayer	Wheat, barley, rapeseed, peas, vegetables, ryegrass, turfgrass		1	0	1
Aerial	Wheat, barley	Fixed wing	1	0	20
		Rotary wing	1	0	20

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

Appendix IV

Table 1 Revised toxicology endpoints

EXPOSURE SCENARIO	ENDPOINT	STUDY	NOAEL/LOAEL (mg/kg bw/day)	UF or MOE
Acute Dietary	teratogenicity (visceral and skeletal effects) with only slight maternal toxicity	oral developmental toxicity - rabbits	32 mg/kg bw/day fenoxaprop-P-ethyl	300
	ARfD = 0.1 mg/kg bw			
Chronic Dietary	haematological and body weight changes, kidney and liver effects	chronic dietary - dogs	0.4 mg/kg bw/day fenoxaprop-ethyl (D/L racemic mixture)	100
	ADI = 0.004 mg/kg bw/day			
Short-Term and Intermediate-Term Dermal (Adults)	Reduced body weight in dams during treatment	Dermal developmental toxicity study - rats	100 mg/kg bw/day	300
Short-Term and Intermediate-Term Inhalation (Adults)	skeletal variations without maternal toxicity	oral developmental toxicity - rats	10 mg/kg bw/day fenoxaprop-P-ethyl	100
Short-Term and Intermediate-Term Dermal (Children)	Adverse liver and kidney effects	Short-term dermal study - rats	20 mg/kg bw/day	100
Short-Term Inhalation (Children)	Adverse liver and kidney effects	28-day inhalation toxicity study - rats	19 mg/kg bw/day	100
Long-Term Dermal and Inhalation	haematological and body weight changes, kidney and liver effects	chronic dietary - dogs	0.4 mg/kg bw/day fenoxaprop-ethyl (D/L racemic mixture)	100
Short-Term Non-Dietary Oral Ingestion	liver and kidney changes	dietary 2-generation reproductive toxicity study - rats	1.5 mg/kg bw/day fenoxaprop-ethyl (D/L racemic mixture)	100
Cancer	$Q_1^* = 8.7 \times 10^{-2}$ (mg/kg bw/day)$^{-1}$			

Table 2 Revised Residential Post-application Non-Cancer Risk Estimate (at Day 0) - turfgrass, recreational areas and residential lawns

Crop	Re-entry activity	Application rate (µg/cm²)	Dislodgeable residue value (µg/cm²)[a]	Transfer coefficient for dermal contact[b] (cm²/hour)	Exposure (mg/kg bw/day)				MOE		
						Oral			Dermal		Non-dietary Oral
					Dermal[c]	Hand-to-mouth[d]	Object-to mouth[e]	Soil ingestion[f]	Adult (Target=300)	Children (Target=100)	Children (Target=100)
Turfgrass, recreational areas and residential lawns	Adult, recreational	0.92 (one application per year	0.046	14500	0.0190571	n/a	n/a	n/a	5247	n/a	n/a
	Young, recreational		0.046	9986	0.0235567	n/a	n/a	n/a	n/a	849	n/a
	Toddler, recreational		0.046	5200	0.0318933	0.0012266	0.0001533[g]	0.00000409	n/a	627	1084
	Youth, golf course		0.046	344	0.0016229	n/a	n/a	n/a	n/a	12324	n/a
	Adult, golf course		0.046	500	0.0013142	n/a	n/a	n/a	76092	n/a	n/a

a 5% of application rate; a maximum of 1 application per year.

b Based on US EPA Policy 12, Standard Operating Procedures (SOPs) for Residential Exposure Assessments, revised February 22, 2001.

c Dermal exposure = DFR × exposure time × transfer co-efficient / (1000 × body weight), (adult, 70 kg, 39 kg youth, child 15 kg). Exposure time of 2 hours for recreation, and 4 hours for playing golf.

d Toddler hand-to-mouth exposure was calculated as per US EPA Policy 12, Standard Operating Procedures (SOPs) for Residential Exposure Assessments, revised February 22, 2001): Hand-to-mouth Exposure = DFR × SA × Hand-to-mouth events × SEF × Duration / (1000 × BW). SA: Surface area of a child's hand is 20cm2 (USEPA, 2001); Hand-to-mouth events: Assumed 20 events/hour with 100% reloading of the hands between each event (USEPA 2001); SEF: Salia extraction factor, assumed 50% (USEPA, 2001); BW: 15 kg for children.

e Toddler object-to-mouth exposure was calculated as per US EPA Policy 12, Standard Operating Procedures (SOPs) for Residential Exposure Assessments, revised February 22, 2001): Object-to-mouth Exposure = DFR × Area of object × SEF / (1000 × BW). Area of Object: A surface area of 25cm2 represents the approximate area from which a child may grasp a handful or grass or "mouth" an object (USEPA, 2001); SEF: Salia extraction factor, assumed 50% (USEPA, 2001); BW: 15 kg for children.

f Toddler soil ingestion exposure was calculated as per US EPA Policy 12, Standard Operating Procedures (SOPs) for Residential Exposure Assessments, revised February 22, 2001): Soil ingestion = Application rate × IRs × F × CF / (1000 × BW). IRs : 0.1 g US EPA SOPs 1997); F: Fraction of ai available in uppermost 1 cm of soil, 100% per cm soil; CF: 0.67cm3/ g soil; BW: 15 kg for children.

g 20% of application rate.

Table 3 Revised Residential Post-Application Cancer Risk Estimate (at day 0) - turfgrass, recreational areas and residential lawns

Crop	Application rate (g ai/ha)	Re-entry activity	Absorbed Daily Dose[a] (mg/kg bw/day)	Lifetime Average Daily Dose[b] (mg/kg bw/day)	Cancer Risk[c]
Turfgrass, recreational areas and residential lawns	92 (1 applications per year).	Adult (recreational)	4.03E-03	1.30E-04	1E-05
		Youth (recreational)	4.99E-03	1.53E-05	
		Toddler (recreational)	7.46E-03	2.29E-05	
		Youth (golf course)	3.44E-04	1.05E-06	9E-07
		Adult (golf course)	2.78E-04	8.967E-06	

[a] Absorbed Daily Dose = daily dermal exposure × dermal absorption value. A time-weighted average (TWA) dislogeable foliar residue (DFR) values were calculated by averaging DFR values (from Table 2) for a 14-day period starting at Day 0. Dermal absorption value = 40%.

[b] LADD = Time weighed average ADD × Number of Days of Exposure × Duration of exposure / (365 days × Life expectancy). Number of Days of Exposure = 14 days; Duration of Exposure: 6 years for toddlers and youth, 63 years for adults; Life expectancy: 75 years

[c] Cancer risk = LADD × Q_1*. A Q_1* value of 0.087 (mg/kg/day) was considered appropriate to use in the cancer risk assessment.

Table 4 Revised Occupational (mixer/loader/applicator) Non-Cancer Exposure and Risk Assessment - turf using high pressure hand wand

Crop	Application Equipment	Application Rate	Area Treated/day[a] (ha)	M/L/A Unit exposure[b] (µg/kg ai)		Daily Exposure[c] (µg/kg bw/day)		MOE[d]	
				Dermal	Inhalation	Dermal	Inhalation	Dermal (target =300)	Inhalation (target = 100)
Turf	Golf courses and recreational and residential lawns, High-pressure handwand (Applicator) (light inhalation)	0.11 g ai/L (max. of 1.14 L/ha of product @ 800 L water/ha)	3750 L/day	2453.52	151.00	14.46	0.89	6916	11236

[a] Area treated per day are based on the PMRA's in-house Exposure Re-evaluation Section default values.
[b] Canadian PHED version 1.1, February 2002.
[c] Dermal exposure = unit exposure × application rate × daily area treated / body weight (70 kg)
Inhalation exposure = unit exposure × application rate × daily area treated / body weight (70 kg)
[d] MOE was calculated as: NOAEL / daily dose

Table 5 Revised Occupational (mixer/loader/applicator) Cancer Risk Estimates - turf using high pressure hand wand

Crop	Application Method	Application Rate	Area Treated Per Day (ha)	Absorbed Daily Dose[a] (µg/kg bw/day)	Lifetime Average Daily Dose[b] (mg/kg bw/day)	Risk[c]
Turf	Golf course, High-pressure handwand (Applicator) (light inhalation)	0.11 g ai/L (max. of 1.14 L/ha of product @ min. 400 L water/ha)	3750 L/day	6.67	1.46E-04	1E-05
	Recreational and residential lawns, High-pressure handwand (Applicator) (light inhalation)	0.11 g ai/L (max. of 1.14 L/ha of product @ min. 400 L water/ha)	3750 L/day	6.67	2.92E-04	3E-05

[a] Absorbed Daily Dose = (daily dermal dose × dermal absorption value) + daily inhalation dose.
Where dermal absorption value = 40%
[b] LADD = ADD × treatment frequency × working duration / (365 days/year × life expectancy (75 years)).
Where treatment frequency = 15 days for golf course; 30 days for custom lawn applicators.
Working duration = 40 years (NAFTA, 1999).
[d] Cancer risk = LADD × Q_1^*. A Q_1^* value of 0.087 (mg/kg/day) was considered appropriate to use in the cancer risk assessment

Table 6 Revised Occupational Post-Application Non-Cancer Risk Estimates, turfgrass – sod farm and golf course

Crop	Application rate (g ai/ha)	Re-entry activity	Transfer coefficient[a] (cm^2/hour)	Dislodgeable residue ($\mu g/cm^2$)	Dermal Exposure[b] (mg/kg bw/day)	MOE (target=300)
Turfgrass, sod farms, golf courses	92	Harvesting	6800	0.046	0.0357	2801
		mowing, transplanting	3500		0.0184	5435
		Scouting, irrigation, fertilizing, aerating, hand pruning, seeding treated turf	500		0.00263	38023

[a] TCs are based on the PMRA's in-house Exposure Re-evaluation Section default values.
[b] Dermal exposure = DFR × exposure time × transfer co-efficient /1000 × Body weight (70 kg).
Where DFR = 5% of application rate for turfgrass; exposure time was 8 hours.

Table 7 Revised Occupational Post-application Cancer Risk Estimates, turfgrass – sod farm and golf course

Crop	Application rate (g ai/ha)	Re-entry activity	Total Absorbed Daily Dose[a] (mg/kg bw/day)	Lifetime Average Daily Dose[b] (mg/kg bw/day)	Cancer Risk[c]
Turfgrass, sod farms, golf courses	92	Harvesting	7.01E-03	1.54E-04	1E-05
		mowing, transplanting	3.62E-03	7.93E-05	7E-06
		Scouting, irrigation, fertilizing, aerating, hand pruning, seeding treated turf	5.15E-04	1.13E-05	1E-06

[a] ADD= daily dermal dose × Dermal absorption value. A time-weighted average (TWA) dislogeable foliar residue (DFR) values were calculated by averaging DFR values (from Table 6) for a
15-day period starting at Day 0. Dermal absorption value = 40%.
[b] LADD = ADD × treatment frequency × working duration / (365 days/year × life expectancy (75 years)).
Where treatment frequency = 15 days for both agricultural and golf course workers. Working duration = 40 years (NAFTA, 1999).
[c] Cancer risk = LADD × Q_1*. A Q_1* value of 0.087 (mg/kg/day) was considered appropriate to use in the cancer risk assessment.

Table 8 Revised Occupational (mixer/loader/applicator) Non-Cancer Exposure and Risk Assessment - potatoes, lentils and flaxes

Crop	Application Equipment	Application Rate (g ai/ha	Area Treated/day[a] (ha)	M/L/A Unit exposure[b] (µg/kg ai)		Daily Exposure[c] (µg/kg bw/day)		MOE[d]	
				Dermal	Inhalation	Dermal	Inhalation	Dermal (target =300)	Inhalation (target = 100)
Personal Protective Equipment: M/L: coveralls over long sleeved shirt, long pants, gloves; A: coveralls over single layer cloth									
Potatoes	Custom applicator M/L (liquid, open). Groundboom, open cab	54	360	53.81	2.56	14.94	0.71	6693	14084
	Farmer applicator M/L (liquid, open). Groundboom, open cab		107	53.81	2.56	4.44	0.21	22523	47619
Lentils, flax	Custom applicator M/L (liquid, open). Groundboom, open cab	37	360	53.81	2.56	10.24	0.49	9766	20408
	Farmer applicator M/L (liquid, open). Groundboom, open cab		107	53.81	2.56	3.04	0.14	32895	69067

[a] Area treated per day are based on the PMRA's in-house Exposure Re-evaluation Section default values.
[b] Canadian PHED version 1.1, February 2002.
[c] Dermal exposure = unit exposure × application rate × daily area treated / (1000 × body weight (70 kg))
Inhalation exposure = unit exposure × application rate × daily area treated / (1000 × body weight (70 kg))
[d] MOE was calculated as: toxicology endpoint / daily dose

Table 9 Revised Occupational (mixer/loader/applicator) Cancer Risk Estimates - potatoes, lentils and flaxes

Crop	Application Method	Application Rate (g ai/ha)	Area Treated Per Day [a] (ha)	Absorbed Daily Dose[b] (µg/kg bw/day)	Lifetime Average Daily Dose[c] (mg/kg bw/day)	Risk[d]
Potatoes	Groundboom (custom)	54	240	4.70	1.03E-04	9E-06
	Groundboom (farmer)		60	1.21	1.76E-06	2E-07
Lentils, flaxes	Groundboom (custom)	37	240	3.22	7.05E-05	6E-06
	Groundboom (farmer)		60	0.83	1.21E-06	1E-07

[a] Based on the 95th percentile of far size from Stats Canada 2006 Census of Agriculture data. Custom applicators were assumed to treat 6 farms per day.

[b] Absorbed Daily Dose = (daily dermal dose × dermal absorption value)+ daily inhalation dose.
Dermal exposure = unit exposure × application rate × daily area treated / body weight (70 kg)
Inhalation exposure = unit exposure × application rate × daily area treated / body weight (70 kg)
Dermal absorption value: 40%

[c] LADD = ADD × treatment frequency × working duration / (365 days/year × life expectancy (75 years)).
Where treatment frequency = 15 days for custom applicators; 1 day for farmer applicators.
Working duration = 40 years (NAFTA, 1999).

[d] Cancer risk = LADD × Q_1*. A Q_1* value of 0.087 (mg/kg/day) was considered appropriate to use in the cancer risk assessment.

Table 10 Revised Occupational Post-Application Non-Cancer Risk Estimates MOEs - flax, broccoli, cabbage and cauliflower

Crop	Application rate (g ai/ha)	Re-entry activity	Transfer coefficient[a] (cm^2/hour)	Dislodgeable residue (µg/cm^2)	Dermal Exposure[b] (mg/kg bw/day)	MOE (target=300)
Flax	37	Scouting	1500	0.074	0.0127	7874
Broccoli, cabbage, cauliflower	54	Irrigation, scouting, thinning	2000	0.108	0.0247	4049

[a] USEPA Policy # 003.1, Agricultural Transfer Coefficients, revised August 7, 2000.
[b] Dermal exposure was calculated as: DFR × application rate × exposure time × transfer co-efficient /1000 × Body weight (70 kg).
Where EDR = 20% of application rate; exposure time was 8 hours.

Table 11 Revised Occupational Post-application Cancer Risk Estimates - flax, broccoli, cabbage and cauliflower

Crop	Application rate (g ai/ha)	Re-entry activity	TWA Absorbed Daily Dose[a] (mg/kg bw/day)	Lifetime Average Daily Dose[b] (mg/kg bw/day)	Cancer Risk[c]
Flax	37	Scouting	1.58E-03	6.93E-05	6E-06
Broccoli, cabbage, cauliflower	54	Thinning	3.07E-03	1.35E-04	1E-05

[a] ADD= daily dermal dose × Dermal absorption value, A time-weighted average (TWA) dislogeable foliar residue (DFR) values were calculated by averaging DFR
values (from Table 6) for a
30-day period starting at Day 0.
Dermal absorption = 40%.
[b] LADD = ADD × treatment frequency × working duration / (365 days/year × life expectancy (75 years)).
Where treatment frequency = 30 days. Working duration = 40 years (NAFTA, 1999).
[c] Cancer risk = LADD × Q_1*. A Q_1* value of 0.087 (mg/kg/day) was considered appropriate to use in the cancer risk assessment.

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